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CELL-THEORY OF DEVELOPMENT

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presented by the author

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THE INADEQUACY OF THE CELL-THEORY OF DEVELOPMENT.[1]

C. O. WHITMAN.

THE doctrine of Schleiden and Schwann that in *cell-formation* lies the whole secret of organic development, has held the place of a central axiom in biological work and speculation for over half a century. All this time the cell has been, as it were, the alpha and omega of both morphological and physiological research. Regarded as a primary element of structure, it has come to signify in the organic world what the atom and molecule signify in the physical world.

The traditional *cell-standpoint* has been most exactly defined by Schleiden and Schwann. In his celebrated "Beiträge zur Phytogenesis" (Müller's Archiv, 1838), Schleiden sets forth the cell-doctrine, which he limited to plants, in the following words : "*Each cell leads a double life ; an independent one, pertaining to its own development alone ; and another incidental, in so far as it has become an integral part of a plant.*"

"The entire plant appears to live only for and through the elementary organ" (cell).

Schwann, in his classical Researches of 1839, extends the same view to the entire organic world.

"*Each cell,*" he affirms, "*is, within certain limits, an individual, an independent whole. The vital phenomena of one are repeated, entirely or in part, in all the rest. These individuals, however, are not ranged side by side as a mere aggregate, but so operate together, in a manner unknown to us, as to produce an harmonious whole.*" (Introduction, p. 2.)

"*The whole organism subsists only by means of the reciprocal action of the single elementary parts.*" (Theory of cells, p. 191.)

The method of reasoning is precisely the same as we have seen in some of the latest experimental studies on cleavage. Witness the following : "If we find that some of these

[1] Read Aug. 31, at the Zoölogical Congress of the World's Columbian Exposition.

elementary parts, not differing from the others, *are capable of separating themselves from the organism*, and pursuing an independent growth, we may thence conclude that each of the other elementary parts, each cell, is already possessed of power to take up fresh molecules and grow; and that, therefore, *every elementary part possesses a power of its own, an independent life, by means of which it would be enabled to develop independently*, IF THE RELATIONS WHICH IT BORE TO EXTERNAL PARTS WERE BUT SIMILAR TO THOSE IN WHICH IT STANDS IN THE ORGANISM. The ova of animals afford us examples of such independent cells, growing apart from the organism." (*l. c.* p. 192).

In these words of Schleiden and Schwann we see no vague anticipation, but a clear statement, of the cell-standpoint of to-day. The organism consists, morphologically, of cells, and subsists, physiologically, by means of the "reciprocal action" of the cells. *Organization* means cellular structure, and *ontogeny* means cell-formation. "*Der gleiche Elementarorganismus ist es, der Thiere und Pflanzen zusammensetzt.*" (Schwann.)

In this "double life," this "harmonious whole," this "reciprocal action" of "elementary organisms," this "operating together in an unknown manner," we see the "cell-state" theory, the "unknown principle of correlation," the "correlative differentiation," the "cellular interaction" of current literature.

Much as we have enlarged our knowledge of the cell, we are still looking at the problems of life from the point of view occupied by the founder of the cell-doctrine. The most notable advances in cytology have but tended to define and emphasize the cell-standpoint. The discovery that *all cells arise by division of preëxisting cells*, neatly embodied in Virchow's maxim, "*omnis cellula e cellula*"; the extension and verification of this maxim furnished by Gegenbaur in 1861, in demonstrating *the vertebrate egg to be a single cell;* and the proof obtained during the last twenty years that the *internal processes of cell-division are fundamentally the same in both plants and animals*, — all these capital steps forward have tended to magnify the importance of the cell as a universal unit of structure.

All higher organization is supposed to begin with cell-formation, and to reach its fullest expression in the mutuality of the constituent cells. Whether the cytoplasm be regarded as isotropic or as definitely organized, whether the hereditary substance be identified with the egg as a whole, or with the nuclear chromosomes alone, the cell-dogma is still supreme.

Our microscopes resolve the organism into cells, and ontogeny shows that the many cells arise from one cell ; hence, the organism seems to be the product of cell-formation, and the cleavage of the germ seems to be a *building* process. The cell-theory points us to very definite units, as the elements of organization, and thus offers what has for a long time appeared to be a rational basis for the investigation of life-phenomena. All the search-lights of the biological sciences have been turned upon the cell ; it has been hunted up and down through every grade of organization ; it has been searched inside and out, experimented upon, and studied in its manifold relations as a unit of form and function. It has been taken as the key to ontogeny and phylogeny, and on it theories of heredity and variation have been built. For a long time it has been regarded as a decisive test of homology in germ-layers, tissues, and organs. Fundamental distinctions have been made between *intra*-cellular and *inter*-cellular organization, between unicellular and multicellular organisms and organs, between cellular and acellular growth and development, between the processes of fission and regeneration in the protozoan and the metazoan, between differentiation *within* the cell and *among* cells, between the formative forces which shape the infusorian and those which act in a many-celled organism.

An organism of many cells is supposed to differ from one of one cell, somewhat as a complex molecule differs from a simple one. The complex unit bears not only the structure of its individual parts, but also a totally new structure formed by the union of these parts. In like manner the organism is fancied to carry at least two distinct organizations, the organization of the separate cells and that of the cells united. The higher organization thus differs, *qualitatively*, from the lower, so that

we may have analogies, but no homology of organs between unicellular and multicellular organisms.

How sharply the line is drawn in this regard is shown in the scrupulous care with which authors avoid the suggestion of anything comparable to muscle or nerve in the infusorian. The Ehrenberg view of infusorian organization demanded altogether too much, and we have swung to the opposite extreme of thinking that the very idea of such comparison is forbidden by the cell-doctrine. Any suggestion of a possible community of origin between an organ — say the *mouth* — of such an animal and the corresponding structure of a cellular organism, would be quickly relegated to the *limbus fatuorum*. Who dares question the proposition that there *can* be no morphological identity between an organ formed without cells and one formed with cells? No matter how complete the physiological correspondence, the two things must be assumed to differ *toto coelo*, as measured by the cell-rule. That is the cell-standpoint.

While the cell-doctrine has been carried steadily forward, confidence in its all-sufficiency has been somewhat shaken from time to time, and a few cautious protests have been ventured against the complete ascendancy of the cell as a unit of organization. Botanists, among whom in this particular the name of Sachs stands foremost, have led the way to another standpoint, which, in contradistinction to the prevailing one, may be called the *organism-standpoint*. Among zoölogists, Rauber has most boldly and ably defended this point of view; and more recently Wilson has expressed similar views, but with reservations that still uphold the cell-standpoint. Driesch, too, obtains experimental proof that "the *mode* of cleavage is something unessential to the future animal," but still he feels compelled to explain the organism from the cell-standpoint, — that is, he supposes that the organism is determined by *correlative* differentiation of homodynamous ("omnipotent") cells or nuclei. The position is altogether similar to that of Oscar Hertwig and Wilson. Wilson, however, holds that the cleavage may secondarily acquire a "mosaic" significance, and herein makes a decided advance towards a pre-organization

theory. *A certain grade of organization as the result of heredity* rather than of cleavage is conceded for annelid development, and for all forms, in so far as future characters are foreshadowed in cleavage stages. This is a limited application of the view which I believe holds true of all eggs, *even before cleavage begins.* It will be easy to show that the very facts generally relied upon to disprove the existence of organization in the egg furnish very strong evidence in support of it.

The question as to the presence of organization is not settled by the *form* of cleavage. Eggs that admit of complete orientation at the first or second cleavage, or even before cleavage begins, are commonly supposed to reflect *precociously* the later organization, while eggs, in which such early orientation is impossible, are supposed to be more or less completely isotropic and destitute of organization. When the region of apical growth is represented by conspicuous teloblasts, the fate of which is seen to be definitely fixed from the moment of their appearance, we find it impossible to doubt the evidence of organization, or "precocious differentiation," as it is conventionally called. When the same region is composed of more numerous cells, among which we are unable to distinguish special proliferating cells, we lapse into the irrational conviction that the absence of definitely orientable cells means just so much less organization.

Cell-orientation may enable us to infer organization, but to regard it as a measure of organization is a serious error. The organization of a vertebrate embryo cannot be said to be less advanced than that of an annelid embryo, because it lacks the unicellular teloblasts which the latter may possess. The regular holoblastic cleavage of the mammalian egg is evidently no index to its grade of organization. The more carefully we compare the cleavage in different eggs, the more clear it becomes that the test of organization in the egg does not lie in its mode of cleavage, but in subtile formative processes. We find the most unlike forms of cleavage issuing in the same remarkable form-phases ; for example, the primitive streak of mammalian and avian eggs ; and conversely, we find identical forms of cleavage leading to fundamentally different

results ; for example, in the egg of the polyclad as compared with that of the mollusc or the annelid, where "*cells having precisely the same origin in the cleavage, occupying the same position in the embryo, and placed under the same mechanical conditions, may nevertheless differ fundamentally in morphological significance.*" (Wilson.)

The most remarkable feature of avian development is the primitive streak. The presence of this feature in typical form, in such an egg as that of the mammal, is certainly one of the most significant facts in embryology. The conclusion is here forced upon us — and I see no escape from it — that the formation of the embryo is not controlled by the form of cleavage. The plastic forces heed no cell-boundaries, but mould the germ-mass regardless of the way it is cut up into cells. That the forms assumed by the embryo in successive stages are not dependent on cell-division, may be demonstrated in almost any egg. Watch the expansion of the blastoderm in the pelagic teleost egg, the formation of the germ-ring, and especially the *axial concentration of material*, which is so beautifully illustrated in these eggs. Such developmental processes are, if I mistake not, clearly indicative of some sort of organization.

The formation of the whole from a part, regarded by some as conclusive evidence of isotropy and correlative *cell*-differentiation, no more disproves the existence of definite organization in the case of the egg than in the case of hydra. A fragment of a hydra may reproduce the whole organism ; and in so doing act as a unit, not as a fraction of a unit. In the same way, one of the first two or four blastomeres, when severed from vital connection with its fellow or fellows, may develop *as a unit, not as a half-unit*, precisely as Wilson insists is the case in Amphioxus.

If the isolated blastomere continues for a while to form cells as if it were a half-unit or a quarter-unit, and only later manifests the whole unit-power of the organism, I see no reason to conclude that the case is fundamentally different. In either case the part has the power of reorganizing itself into the whole, and it makes no essential difference whether the reor-

ganization be accomplished at once, before cells are formed, or gradually, while cell-formation is going on.

If we no longer hesitate to accept Brücke's view that the functions of the cell are proof of organization, although our best microscopes fail to give us any idea of what it consists in, it certainly ought not to be difficult to regard the egg as a young organism, and the developmental phenomena as proof of organization. Such organization is, in fact, conceded when we speak of the egg as the rudiment of an organism ("Anlage eines Organismus," O. Hertwig), but, nevertheless, we go on insisting that cellular structure is the essence of a higher organization.

We are so captured with the personality of the cell that we habitually draw a boundary-line around it, and question the testimony of our microscopes when we fail to find such an indication of isolation. We have so long insisted on these boundary-lines as limiting homologies that we find it extremely difficult to ignore them. How difficult it is, for example to regard a multicellular nephridial funnel as the exact homologue of the unicellular funnel. If the organ consist of one cell, the tube is *intra*-cellular ; if of many cells, then it is *inter*-cellular. But we have the "tube" and the "flame" just as perfect with one cell as with many, as Vejdovsky's studies make very certain. How idle, then, to deny homology between two such organs merely because one is *intra-* and the other *inter*-cellular. And yet that is precisely what we have been accustomed to do.

Now this one case illustrates, as I believe, a general truth of no little importance. *The nephrostome is a nephrostome all the same whether it consist of one cell, two cells, or many cells. Its form and function are both independent of the number of component cells. Cells multiply, but the organ remains the same throughout. So far as homology is concerned, the existence of cells may be ignored.*

May we not go further, and say that an organism is an organism from the egg onward, quite independently of the number of cells present? In that case *continuity of organization* would be the essential thing, while division into cell-territories might

be a matter of quite secondary importance. As the nephrostome is not the result of cell-formation, but exists as such before division into cells, so the organism exists before cleavage sets in, and persists throughout every stage of cell-multiplication. Continuity of organization does not of course mean preformed organs, it means only that a definite *structural* foundation must be taken as the starting-point of each organism, and that the organism is not multiplied by cell-division, but rather continued as an individuality through all stages of transformation and sub-division into cells.

We have long been aware that the cell could not be taken as the ultimate unit of life, and every notable effort to account for heredity has led to the postulation of primary elements in comparison with which the cells appear as complex organisms. Since Ernst Brücke first contended for the organization of the cell in 1861, and the existence of "smallest parts" as the basis of this organization, we have seen similar ideas reappear in the "physiological units" of Herbert Spencer, the "gemmules" of Darwin, the "micellae" of Nägeli, the "plastidules" of Elsberg and Haeckel, the "inotagmata" of Th. Engelmann, the "pangens" of de Vries, the "plasomes" of Wiesner, the "idioblasts" of Oscar Hertwig, and the "biophores" of Weismann.

After the discovery of cell-division as the law of cell-formation, and after the scheme of the cell set up by Schleiden and Schwann had been revised and reduced to essentialities by Leydig, Max Schultze, and others, the next great step forward in the cell-doctrine must be credited to Brücke, who, seeing that the phenomena of life could not be referred to a *structureless* substance, declared for the *organization* of the cell in words that were scarcely less than revolutionary.

"We must therefore," says Brücke, ascribe to living cells, in addition to the molecular structure of the organic compounds which they contain, still another, and otherwise complicated, structure; and this it is that we designate by the name organization."

Further, in his own words: "*Wir müssen in der Zelle immer einen kleinen Thierleib sehen, und dürfen die Analogien, welche zwischen ihr und den kleinsten Thierformen existiren, niemals aus den Augen lassen.*" (Elementarorganismen, p. 387.)

On the botanical side, Sachs has maintained since 1865 ("Experimental-Physiologie") that protoplasm is an "*organized body*" (*cf.* Lectures on Physiology, 1887, p. 206–7). While Brücke contended for organization *within* the cell, and remained true to the cell-theory of all higher organization, Sachs, Goebel and some other botanists early challenged the doctrine of cell-hegemony. Sachs briefly indicates his standpoint in the following words :

"To many, the cell is always an independent living being, which sometimes exists for itself alone, and sometimes 'becomes joined with' others — millions of its like, in order to form a cell-colony, or, as Haeckel has named it for the plant particularly, a cell-republic. To others again, to whom the author of this book also belongs, cell-formation is a phenomenon very general, it is true, in organic life, but still only of *secondary significance;* at all events, it is merely one of the numerous expressions of the formative forces which reside in all matter, in the highest degree, however, in organic substance." (Lectures, etc., p. 73.)

Brücke's great merit consists in this, that he taught us the necessity of assuming *structure* as the basis of vital phenomena, in spite of the negative testimony of our imperfect microscopes. That function presupposes structure is now an accepted axiom, and we need only extend Brücke's method of reasoning, from the tissue-cell to the egg-cell, in order to see that there is no escape from the conclusion that the whole course of developmental phenomena must be referred to organization of some sort. *Development, no less than other vital phenomena, is a function of organization.*

Nägeli followed the same method of reasoning when he concluded that the organism was, in a certain sense, "vorgebildet" in the germ-cell (Beiträge zur wiss. Botanik, Heft II. 1860). This point of view is well expressed in his classical work, the "Theorie der Abstammungslehre," where he says : "Organisms differ from one another as egg-cells no less than in the adult state. The species is contained in the egg of the hen as completely as in the hen, and the hen's egg differs from the frog's egg just as widely as the hen from the frog."

While all will admit that the organization of the egg is such as to predetermine the organism, few will be prepared to admit that *the adult organization is identical in its* INDIVIDUALITY

with that of the egg. The organism is regarded rather as a community of such individualities, bound together by interaction and mutual dependence. According to this view, development does not consist in carrying forward continuous changes in the same individual organization, but in multiplying individualities, the complex of which represents, at every stage, not *the* organism, but one of an ascending series of organisms, which is to terminate in the adult form.

In the egg-cell we are supposed to have an *elementary* organism ; in the two-cell stage, two elementary organisms, forming together an organism of a totally different order, based on a new scheme of organization. In the four-cell stage we have another organism, in the eight-cell stage another, and so on.

"Physiological division of labor," as Milne-Edwards first phrased it, is unquestionably a principle of wide application. Given the cells as morphological units and this physiological principle, the evolution of a cellular organism, may be conceived of as a most simple affair. From a simple colony of like cells, we pass to a commonwealth of differentiated and mutually dependent cells. A multitude of independent cell-organisms, adopting mutual service as the best economy, find themselves in the end incapable of independent life, and so firmly bound together in interdependence, that they constitute a complex individual. The usual conception of this division of labor is, as Herbert Spencer[1] has recently stated it, "an *exchange of services,* — an arrangement under which, while one part devotes itself to one kind of action, and yields benefits to all the rest, all the rest, jointly and severally performing their special actions, yield benefits to it in exchange. Otherwise described, it is a system of *mutual* dependence."

We habitually apply this anthropomorphic conception to every grade of organization. The higher organism is regarded as a colony of cells ; the cell as a colony of simpler units, nucleus, centrosome, and so on ; the nucleus as a colony of chromosomes ; the chromosome, according to Weismann's terminology, as a colony of "ids"; the "id" as a colony of

[1] The Contemporary Review, February, March, and May, 1893.

"determinants"; the "determinant" as a colony of "biophores," and the "biophore" as a colony of molecules.

In proportion as division of labor is carried out, *interdependence* is increased, and the units become more and more intimately associated. The struggle for existence is supposed to extend to the cells, and even to the biophores. Symbiotic relations are fought out, refined, and confirmed by natural selection, and eventually reduced to a system of mutual adaptations which are fancied to be the basis of organic unity.

Whether organization is wholly a matter of acquisition, and whether it became possible only as a result of symbiotic advantages accidentally discovered in the struggle for existence, need not here be discussed. It is enough for present purposes to know that organization exists, and that *organic* unity depends on *intrinsic properties* no less than does *molecular* unity.

It is not division of labor and mutual dependence that control the union of the blastomeres. It is neither functional *economy* nor social instinct that binds the two halves of an egg together, but the constitutional bond of *individual organization.* It is not simple adhesion of independent cells, but integral structural cohesion.

That organization precedes cell-formation and regulates it, rather than the reverse, is a conclusion that forces itself upon us from many sides. In the infusoria we see most complex organizations worked out within the limits of a single cell. We often see the formative forces at work and structural features established before fission is accomplished. Cell-division is here plainly the result, not the cause, of structural duplication. The multicellular Microstoma behaves essentially in the same way as the unicellular Stentor, or the multinucleate Opalinopsis of Sepia. The Microstoma organization duplicates itself, and fission follows. The chain of buds thus formed bears a most striking resemblance to that of Opalinopsis, and the resemblance must lie deeper in the organization than cell-boundaries.

Compare the results obtained by artificial division in two such forms as Stentor and Hydra. The two courses of regen-

eration are so exactly parallel that one cannot fail to see at once that the formative forces operate in essentially the same manner with the one-celled as with the many-celled organism. Gruber's experiment, as described in his recent article, "*Microscopic Vivisection*" (Berichte der Naturforschenden Gesellschaft zu Freiburg, Vol. VII, Part 1, 1893), illustrates well this point.

A Stentor was cut into three pieces, *A*, *B*, *C*, each of which regenerated the missing parts within 24 hours. The anterior

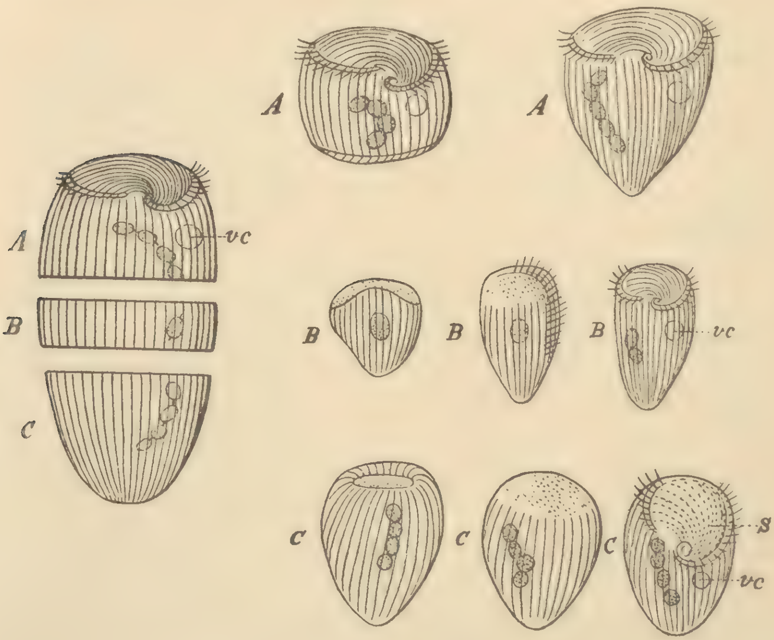

FIG. 1.— Regeneration of a Stentor cut into three parts, *A*, *B*, *C*. *vc* = pulsating vacuole. *S* = regenerating frontal field.

end regenerated posterior end, and *vice versa*. The middle piece regenerated both ends — the complicated frontal field with its mouth, pharynx, long cilia, pulsating vesicle, *etc.*, as well as the simpler posterior region.

Treat a Hydra in the same way and similar results will follow. In both cases the orientation of the parts will remain the same as that of the whole. Gruber repeated the division of Stentor four times in succession, getting perfect regeneration each

time, but *smaller* individuals, as no growth was possible. The experiment reminds one of the half- or quarter-sized embryos obtained by separating the first two or four blastomeres.

Gruber's highly interesting paper calls attention to the identity in form and structural detail of the "membranellae" of Stentor with the so-called "corner-cells" (Eckzellen) of molluscs (*Cyclas cornea*). The comparison is a most instructive one, illustrating in the most conclusive manner that differentiation of the parts of the *soma* depends, not on the interaction of cells, but upon the elementary structure of the protoplasm.

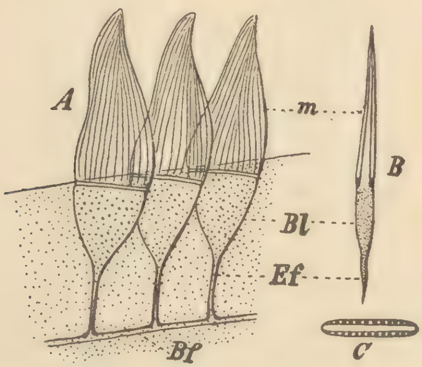

FIG. 2. — *A*, three membranellae of Stentor, *B*, membranella in section. *C*, Section at the base of the two plates. *Bl*, Basal lamella. *Ef*, Terminal fibre. *Bf*, Basal fibril. *K*, Nucleus.

The membranellae of the frontal field of Stentor consist of two thin, adherent plates, each of which represents a number of coalesced cilia. The structure has a basal seam or ridge[1] (Leiste), and a basal lamella which is continued into a terminal fibre. All these fibres are connected by the basal fibril, through which the movements of the membranellae are evidently regulated.

Now this highly differentiated organ, the membranella, is reproduced with most remarkable exactness in the "corner-cell" of Cyclas. But here the organ represents an individual

[1] This seam consists of a series of microsomes, as Dr. Watase has discovered.

cell, while in Stentor a whole crown of such organs is formed without any division into cells. Could one ask for a clearer demonstration? Are we not forced to conclude with Gruber that "*however great the difference between an infusorium and a highly organized animal, it cannot be a qualitative one. We can assume that the same vital elements serve in both as the foundation, only in ever new combinations. This kinship declares itself very clearly in the correspondence of many organs of the infusoria with those of the higher organisms*" (*l.c.* p. 16).

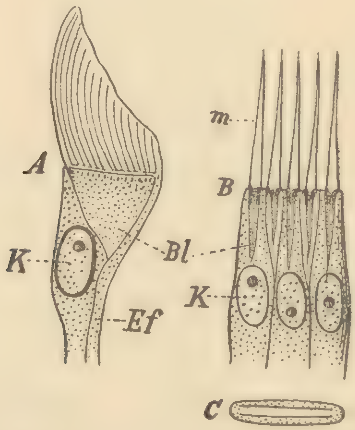

FIG. 3.— *A*, "Corner cell" of *Cyclas cornea*. *B*, Section of three cells. Other letters as in Fig. 2.

"So finden wir," says Gruber, "in einem Thiere, das schon hoch auf der Stufenleiter der vielzelligen Organismen steht, dieselben Grundelemente wieder wie in dem einzelligen Infusionsthierchen. . . .

"Wieder und wieder der Beweis von dem göttlich einfachen aber auch göttlich gewaltigen Gesetze der *Einheit der Natur*" (p. 18).

The entoderm of Dicyema illustrates one or two points of interest in this connection. We have here an organ in which, as often happens, in parasitic degradation, cell-formation has been dispensed with. The entoderm remains throughout life as a single cell, and the whole process of reproduction, for both kinds of embryos, is carried on *in the body of this cell* without any cellular organs whatever.

In one respect this unicellular organ, which was undoubtedly once multicellular,

What is the difference between an organization embracing one cell and one embracing two or many cells? Certainly the essential difference cannot lie in the *number* of cells. We must look entirely behind the cellular structure for the basis of organization. Even a highly differentiated organism may reach a relatively late stage of development just as well without cell-boundaries as with them, as we see so well illustrated in the insect egg. If we fall back on the number of nuclei as the essential thing, then we shall have to reckon with multinucleate infusoria. In these forms do we not see that it is always the *same* organism before us, as we follow its history through the whole cycle of nuclear phases?

The essence of organization can no more lie in the number of nuclei than in the number of cells. The structure which we see in a cell-mosaic is something superadded to organization, not itself the foundation of organization. Comparative embryology reminds us at every turn that the organism dominates cell-formation, using for the same purpose one, several, or many cells, massing its material and directing its movements, and shaping its organs, as if cells did not exist, or as if they existed only in complete subordination to its will, if I may so speak.

In the phenomena of regeneration and embryogenesis we find abundant evidence. For the present I must limit myself to a few features of development.

Perhaps the peculiar formation of the embryo Toad-fish (Batrachus) is as instructive a case as I am acquainted with.

is quite unique, for it may become the receptacle of nuclei belonging originally to other cells; in other words, *it becomes multinucleate, not by the multiplication of its own nucleus, but by the acquisition of exotic nuclei.*

The acquired nuclei are what I have called elsewhere the "residual" nuclei, which are left over when the formation of "infusoriform embryos" ceases. Each of these nuclei enters into vital relations with the cell, *and each undergoes the differentiations characteristic of the true entoderm nucleus,* so that in the end they can only be distinguished by their positions. This seems to show that the differentiation of nuclei may be controlled by the cell to which they are transplanted.

One of Boveri's observations* shows that the same may be said of the chromosomes. One or more of the chromosomes, normally eliminated in the polar globules, are sometimes carried into the cleavage-nucleus. The supernumerary chromosomes here undergo the regular transformations, quite unlike those which they show when carried out in the polar globule.

* Zellen-Studien. Heft 2, pp. 171-175.

If one will take the trouble to compare this formation with the ordinary type of teleostean development, he will not fail to see that the organizing forces, whatever they may be, operate to form an embryo under peculiar difficulties. It will be seen towards the end of embryogenesis that the material of the germ-ring, owing to the enormous size of the egg, has to travel over quite a long distance, in order to reach the embryo. A very thin bridge of cells connects the hind end of the embryo with the closing germ-ring, and this bridge is formed by the migrating cells of the germ-ring. What determines this wholly exceptional movement of the cell-material required to form the embryo? Is it possible that the cells move as so many independent individualities? But they do move, and no doubt in obedience to directing influences, acting, not in the cells as individuals, but in and through the entire formative material, irrespective of cells.

Whoever doubts this would do well to study more faithfully the *living* embryo during its formation. If the cell-ghost should still haunt his vision, I would suggest still another field for study. I would suggest first of all that he try to get as clear a notion as possible of the formation of the archenteron in Amphioxus, Petromzyon, and the Frog. The case of the reptile might then be studied with profit. Next the "chorda-canal" of mammals, and finally Kupffer's vesicle in the teleost.

There is no longer any doubt in my mind — and here I am in accord with most authorities on this subject — that this little vesicle is a reminiscence of the archenteron. The development of Gecco, as traced by Ludwig Will, removes, as I think, the last doubt on this point.

If the development of Kupffer's vesicle be studied in the light of its phylogenetic significance, and studied in the *living* as well as the dead egg, I cannot help thinking that candid reflection on the facts will be sufficient to force conviction to the standpoint here taken.

Having learned the meaning of the vesicle, one should trace step by step its mode of origin in the pelagic fish-egg. Here one may see this remnant of an archenteric cavity arise, not

inside the embryonic tissues as in the eggs of fresh-water fishes, but actually outside the tissues on the inner face of the embryo, near its posterior end. Its whole ventral and lateral boundary is formed, not by archenteric cells, but by a periblastic layer often as thin as the wall of a soap-bubble, and completely free from all nuclei. It does not even arise as a single cavity, but as numerous minute cavities that look like a cluster of granules. These expand, flow together gradually, and finally form one bubble-like vesicle projecting almost wholly into the transparent yolk. Having attained a maximum size, its slightly concave roof becomes more and more deeply hollowed out, and thus it comes to inclose more and more the cavity, while the latter gradually shrinks in size, and finally vanishes as the true cell-walls close up. Such is briefly the history of this floor-less form-reminiscence of what is a more substantial rudiment in many other embryos.

This remarkable reproduction of a form-phase that is to last only for a few hours and then pass away without leaving a visible trace of its existence, cannot be explained as due to cell-formation nor as the result of *individual* action or interaction on the part of the cells. The embryonic mass acts rather as a *unit*, tending always to assume the form peculiar to the state of development reached by its "essential architectonic elements" (Brücke) — elements that are no less real because, like the atom and molecule, they are too minute to be seen by the aid of our present microscopes.

That cells as such do not participate in this formative act, is shown by the mode of development of the vesicle and by the absence of cells in its ventral and lateral walls. This fact, the absence of cells, has actually been urged recently against the identity of the structure with Kupffer's vesicle, — an error which one is likely to fall into only while under the delusion that acellular walls cannot be homologous with cellular walls.

The evidence furnished by Kupffer's vesicle will doubtless lose much of its force with those who have not had an opportunity to study the subject sufficiently to form an independent opinion about it. To some who are better acquainted with the structure, its meaning may still appear to be somewhat prob-

lematical, and the evidence drawn from it as therefore unsatisfactory. It would be useless in such a case to urge the point, and also wholly needless, as examples abound that are not open to such objections.

The form-changes by which the fish blastodisc passes into the germ-ring stage are examples of this kind. It is well known that the transformation of the blastodisc just before the appearance of the germ-ring is quite rapid, at least in the pelagic fish-egg, and also *quite independent of cell-formation.* The discoidal germ-mass suddenly thins out, but not uniformly in all parts. The half of the disc in which the embryo is to be formed remains thick, anticipating as it were the axial concentration which is to follow, while the half lying in front of this is rapidly reduced to a thin epithelial membrane. This *regional* differentiation of the outer layer and the concomitant formation of the germ-ring, including the forward movement of the embryonic plate ("head process"), which advances in an axial direction to the very centre of the disc, are indubitably accomplished, not by the aid of cell-formation, but by formative processes of an unknown nature, but nevertheless real and all-controlling. Cell-formation, to be sure, goes on, but it seems to me certain that it has no *directive* influence on the formative processes. The cleavage runs on from beginning to end, regularly or irregularly, without modifying in any essential way the form of the blastodisc. All at once, when this segmentation has been carried to a certain point, the transformation sets in and goes rapidly on, without interrupting cell-formation, but to all appearance quite independently of it.

In the axial concentration of the very broad embryonic plate we see a formative process that can have nothing whatever to do with cell-division. Again, in the establishment of the caudal end of the embryo, long before that part of the germ-ring which represents, historically at least, this end can be brought into place, we have another decisive test of formative power asserting itself, not only independently of cell-division, but also against all the obstructions interposed by the yolk. This prepotency of the "plastic power" (Schwann) is seen to great

advantage in the pelagic fish-egg, but still better in the Toad-fish-egg. It is needless to cite further examples of this sort, for the embryology of every animal is full of them, and no one can fail to find who looks for them.

If the formative processes cannot be referred to cell-division, to what can they be referred? To cellular interaction? That would only be offering a misleading name for what we cannot explain ; and such an answer is not simply worthless, but positively mischievous, if it put us on the wrong track. Loeb's experiments in heterogenesis furnish a refutation of the interaction theory. The answer to our question may be difficult to find, but we may be quite certain that when found it will recognize the regenerative and formative power as one and the same thing throughout the organic world. It will find, as Wiesner has so well insisted, a common basis for every grade of organization, and it will abolish those fictitious distinctions we are accustomed to make between the formative processes of the unicellular and multicellular organisms. It will find the secret of organization, growth, development, not in cell-formation, but in those ultimate elements of living matter, for which *idiosomes* seems to me an appropriate name.

What these idiosomes are, and how they determine organization, form, and differentiation, is the problem of problems on which we must wait for more light. All growth, assimilation, reproduction, and regeneration may be supposed to have their seat in these fundamental elements. They make up all living matter, are the bearers of heredity, and the real builders of the organism. Their action and control are not limited by cell-boundaries. As Heitzmann and others have long insisted, the continuity of these elements is not broken by cell-walls. The organization of the egg is carried forward to the adult as an unbroken physiological unity, or individuality, through all modifications and transformations. The remarkable inversions of embryonic material in many eggs, all of which are *orderly* arranged in advance of cleavage,[1] and the interesting pressure experiments of Driesch by which a new distribution of nuclei is *forced* upon the egg, without any sensible modification of the

[1] As will be shown later.

embryo, furnish, as I believe, decisive proof of a definite organization in the egg, prior to any cell-formation. The opinion expressed by Huxley in his review of "The Cell-Theory," in 1853, forms a fitting conclusion to this introductory sketch.

"They [the cells] are no more the producers of the vital phenomena than the shells scattered along the sea-beach are the instruments by which the gravitative force of the moon acts upon the ocean. Like these, the cells mark only where the vital tides have been, and how they have acted."[1]

[1] British and Foreign Medico-chirurgical Review, Vol. XII, p. 314. Oct., 1853.